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Anti-inflammatory effects of different statins in rheumatoid arthritis; a randomized double-blind controlled clinical trial

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Abstract

Introduction: Statin family drugs are lipid-lowering agents with anti-inflammatory effects.
Objectives: The aim of our study was to evaluate anti-inflammatory effects of different statins in rheumatoid arthritis patients.
Patients and Methods: Around 161 eligible subjects with rheumatoid arthritis were enrolled. They randomly were divided into three groups. The first group received 40 mg/daily atorvastatin, the second group received 40 mg/daily simvastatin, and the third group received placebo as control for six months. To calculate the disease activity, DAS-28 (Disease Activity Score 28) was used while VAS (visual analog scale) was used to assess the severity of pain in rheumatoid arthritis patients. DAS-28, erythrocyte sedimentation rates (ESR) and lipid profiles were assessed once for the baseline and then after three and six months of intervention. Data was analyzed by SPSS by a *P* value <0.05 which was set to be significant.
Results: DAS-28 score in months 0, 3 and 6 in atorvastatin, simvastatin and placebo groups was (5.36 ± 1.02, 3.23 ± 1.24 and 2.81 ± 1.13), (5.29 ± 0.87, 2.75 ± 1.16 and 2.57 ± 1.00) and (5.52 ± 0.96, 3.90 ± 1.10 and 3.87 ± 1.52), respectively. Mean of DAS-28 score differences between placebo and atorvastatin groups was 0.6 ± 0.16 ($P<0.01$); the score differences between simvastatin and placebo was 0.900±0.16 that was significant ($P<0.01$), however, the score differences was not significant between atorvastatin and simvastatin groups ($P=0.261$).
Conclusion: Statins decrease inflammation in rheumatoid arthritis patients.
Trial Registration: Registration of randomized double-blinded clinical trial has been approved (approval date; 2008-11-22) in Iranian registry of clinical trial (identifier: IRCT138811161778N2; https://en.irct.ir/trial/1354) (local ethics committee reference number#188099).

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Introduction

The hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins have been used as drugs for reducing serum lipids for many years. In several studies, the utility of statins in reducing renal disease and cardiovascular events has been proven (1,2). In previous studies, evidence of anti-inflammatory effects of statins has been reported (3-5). The mechanisms of anti-inflammatory effects of statins include the inhibition of pro-inflammatory cytokine, chemokine production, adhesion molecule expression, and matrix metalloproteinase (MMP) secretion (6-11). In the other hand, statins can suppress interferon-α/β (IFNα/β)–inducible expression of class II major histocompatibility complex (MHC) molecules as well as class II MHC–dependent activation of T lymphocytes in vitro (12,13). Statins also decrease CD40 and CD40 ligand expression in various cell types, like endothelial cells, smooth muscle cells, and macrophages (14-16). Some kinds of statins that are commonly used for the treatment of hypercholesterolemia can block lymphocyte function–associated antigen1–mediated cell adhesion and co-stimulation

Key point

In RA, the use of statins reduces inflammation and also the disease activity.

of T lymphocytes (17). This evidence suggests the effects of statin suppressant effects on the immune system (18,19). In some experimental autoimmune encephalomyelitis, a CD4 T cell–mediated disease model of multiple sclerosis, atorvastatin prevents or reverses chronic and relapsing paralysis (20,21). Additionally, lovastatin improved the clinical symptoms of experimental autoimmune encephalomyelitis in rats (22).

Rheumatoid arthritis is a chronic inflammatory disease that affects 1% of the population and is associated with some morbidity and mortality (23,24). Rheumatoid arthritis is characterized by symmetric poly-articular inflammation disease that may be directed to joint damage. The pathogenesis of rheumatoid arthritis is not completely understood and there are many cellular and molecular mechanisms for rheumatoid arthritis in recent years (25).

The cells involving in synovial inflammation include, monocyte–Macrophage system, activated T cells and neutrophils and so an increased expression of pro-inflammatory mediators and MMPs (25). Mortality in rheumatoid arthritis patients is higher than that in the general population that is due mainly to premature cardiovascular disease. Cardiovascular risk factors can not entirely explain the higher level of cardiovascular complications, and there is evidence that chronic inflammation is the main offender. The anti-inflammatory effects of statins suggest that statins can be useful in the treatment of rheumatoid arthritis. Simvastatin has recently been reported to improve the course of collagen-induced arthritis in mice (26). In mice, intraperitoneally administration of 40 mg/kg/d simvastatin can control arteritis both in the prevention and after the onset of clinical symptoms. Lower doses of simvastatin (10 or 20 mg/kg) had no significant effect.

Objectives

This study aimed to compare anti-inflammatory effects of atorvastatin and simvastatin on disease activity of rheumatoid arthritis.

Patients and Methods

Patient selection

Rheumatoid arthritis patients were selected from rheumatology clinic of Alzahra hospital of Isfahan, according to criteria of the American College of Rheumatology-1987, with at least three months duration of disease. A total of 162 patients were evaluated for eligibility and met the inclusion criteria and participated in the study. Exclusion criteria were age <18 years, current treatment with lipid-lowering drugs, contraindication to statins, renal or liver failure, pregnancy, discontinue or irregularly taking medications and cancer. Over the study period, one patient was excluded from the research due to irregular use of drugs. Therefore, 161 participants completed the study (Figure 1).

Clinical study and interventions

This was a randomized double-blind controlled clinical trial performed in the rheumatology clinic of Al-Zahra hospital of Isfahan, Iran as of April 2010 to April 2011. They were randomly divided into three groups by computer. The first group received 40 mg atorvastatin, the second group received 40 mg simvastatin, and the third group received placebo. This treatment lasted for six months. For treatment of underlying illness, all patients received the same treatment including methotrexate 7.5 mg weekly, folic acid 1 mg daily, hydroxychloroquine 200 mg daily, prednisolone 5 mg daily, carbonate calcium 1000 mg daily and 25hydroxyvitamin D (25[OH]D) 800 international units daily.

At the first step before intervention, the patients were referred to the reference laboratory while they were for 12 hours in fasting status. After taking samples, we put them in the form of a blood clot (blood clots at room temperature), and it was centrifuged at 35000 rpm for 10 minutes. Around 200 lambdas of these serum samples placed in the cup of the machine. The Pars Azmoon kit was used to determine the serum lipids level factors including triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) and also total cholesterol. Erythrocyte sedimentation rate (ESR) and fasting blood sugar (FBS) of patients were also measured. To calculate the disease activity, DAS-28 (Disease Activity Score 28) was used while VAS (visual analog scale) was used to assess the severity of pain in rheumatoid arthritis patients. Accordingly, a DAS-28 less than 2.6 indicates remission, whereas a value ≥2.6 suggests active disease. These tests were repeated 3 and 6 months after the intervention.

Ethical issues

The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study was approved by the institutional ethics committee of Isfahan University of medical sciences and was registered in Iranian registry of clinical trial (identifier: IRCT138811161778N2; https://en.irct.ir/trial/1354) (local ethics committee reference number#188099). Written informed consent was obtained from all participants.

Statistical analysis

Our study data was analyzed by SPSS software v.16. Values are expressed as means ± standard deviations (SD) or percentages in text and figures. For variables with normal distribution and homogeneity of variance, an independent *t* test and one-way ANOVA was applied for testing differences between two or more groups. For skewed variables, nonparametric Kruskal-Wallis-(H) test or Mann-Whitney U test was applied. The effect of atorvastatin in vivo was evaluated using a paired-sample *t* test or Wilcoxon signed-rank test within groups, depending on normality. For the ranked data, Pearson's

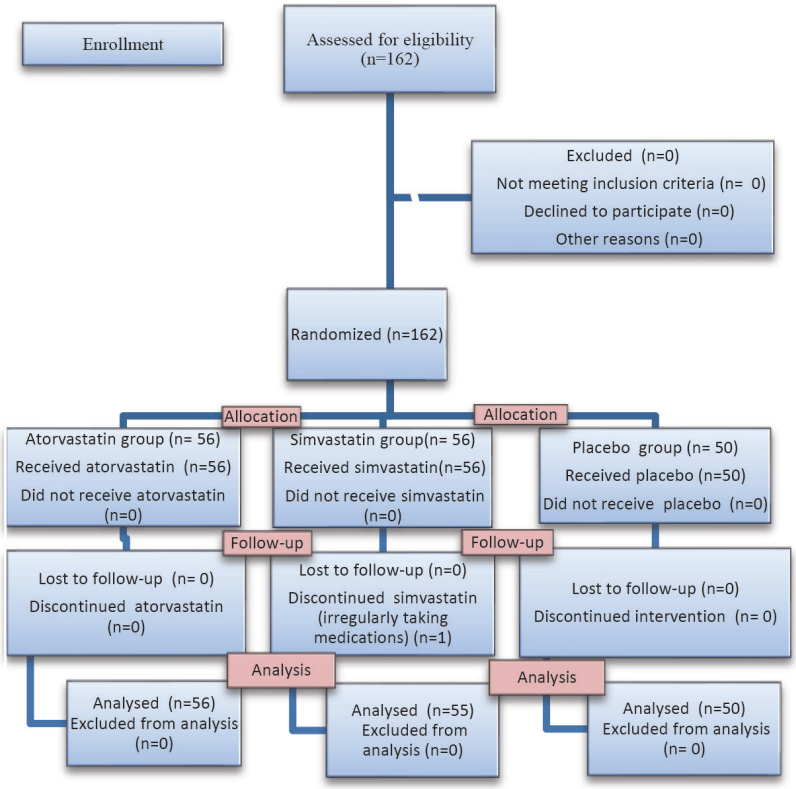

Figure 1. Flow chart of enrollment and allocation of participants and study design (Consort).

chi-square test or Fisher's exact test was applied for the comparison among multiple groups. In all cases, a two-tailed *P* value of <0.05 was respected significant.

Results

Table 1 shows the baseline demographic and clinical characteristics of the subjects with rheumatoid arthritis. Body mass index (BMI) was not different between the three groups. Mean average age in atorvastatin, simvastatin and placebo group was, 46.85 ± 14.12 years, 48.41 ± 12.67 years and 48.60 ± 13.90 years, respectively ($P > 0.05$). The data of DAS-28 in three groups in months 0 and 3 and 6 are shown in Table 2. DAS-28 score overall in baseline, months 3 and 6 in three groups was summarized in Table 3. Mean of DAS-28 score differences between placebo and atorvastatin groups was 0.6 ± 0.16 ($P < 0.01$); the score difference between simvastatin and placebo was 0.900±0.16 that was significant ($P < 0.01$), however, the score difference was not significant between atorvastatin and simvastatin groups ($P = 0.261$).

Table 1. Demographic characteristics of patients according to different groups

	Atorvastatin	Simvastatin	Placebo
Gender			
Male	5	8	8
Female	51	47	42
Total	56	55	50

Discussion

The results of this study showed statins can decrease disease activity of rheumatoid arthritis. Statins act as immunomodulatory drugs that prevent the linkage of T cells to antigen-presenting cells, preventing MHC-II presentation, T-cell activation, inhibiting T-cell proliferation, and down-regulating Th1 cell function (27). Previous experimental or clinical investigations have detected that statins regulate immune responses and can be administered to treat inflammatory processes (28–31). While statins are not a usual treatment for rheumatoid arthritis, various evidence demonstrated that statins have favorable impacts against various features of the disease containing endothelial function, inflammatory status and disease activity (32). A recent study as a double-blind, placebo controlled trial on the administration of atorvastatin in rheumatoid arthritis indicated that atorvastatin is an actually tremendous candidate agent for rheumatoid arthritis patients for decreasing both systemic inflammatory activity and rheumatoid arthritis disease activity, which were measured by DAS-28 and high sensitive-CRP, respectively (33). Conversely, another investigation revealed that statins do not have any advantageous impact to diminish inflammatory process (34). The advantageous properties of statins in rheumatoid arthritis individuals was confirmed in this investigation, as detected by reduced DAS-28 score. Many studies emphasized the effects of statins in native and acquired immune response via activation of endothelium

Table 2. The results of study according to different groups

Parameter	Time of measurement	Atorvastatin	Simvastatin	Placebo	Mean difference betweeplacebo and atorvastatin	*P* value	Mean difference between placebo and simvastatin	*P* value	Mean difference between atorvastatin and simvastatin	*P* value
DAS-28	Baseline	5.36±1.02	5.29±0.87	5.52±0.96	0.161	0.766	0.232	0.513	0.070	0.972
	After 3 moths	3.23±1.24	2.75±1.16	3.90±1.10	0.671	0.012	1.14	0.000	0.473	0.103
	After 6 moths	2.81±1.13	2.57±1.00	3.87±1.52	1.05	0.000	1.29	0.000	0.239	0.667
VAS	Baseline	51.25±21.46	47.54±19.43	55.19±22.04	3.94	0.705	7.65	0.17	3.70	0.732
	After 3 moths	20.44±17.79	16.18±13.87	27.50±17.20	7.05	0.082	11.31	0.002	4.26	0.432
	After 6 moths	15.89±14.68	13.45±10.53	27.70±21.50	11.80	0.001	14.24	0.000	2.43	0.809

DAS-28, disease activity score 28; VAS; visual analog scale.

Table 3. Means DAS-28 according to different groups and gender

Group		DAS-28 mean		
		Base line	After 3 months	After 6 months
Atorvastatin	Female	5.38±0.96	3.35±1.20	2.84±1.11
	Male	5.07±1.62	1.99±1.08	2.47±1.38
	Total	5.36±1.02	3.23±1.24	2.81±1.13
Simvastatin	Female	5.26±0.90	2.88±1.19	2.58±0.97
	Male	5.42±0.65	2.04±0.70	2.49±1.23
	Total	5.29±0.87	2.75±1.16	2.57±1.00
Placebo	Female	5.51±1.01	3.90±1.13	3.90±1.61
	Male	5.70±0.61	3.88±0.99	3.72±0.92
	Total	5.52±0.96	3.90±1.10	3.87±1.52
Total	Female	5.38±0.96	3.36±1.24	3.07±1.35
	Male	5.44±0.93	2.70±1.27	2.95±1.26
	Total	5.39±0.95	3.27±1.25	3.06±1.34

DAS-28, disease activity score 28.

macrophage, neutrophils and natural killer cells (35). The same effects on acquired immune response have shown via inhibition antigen express and polarization of T cells. Statins, both in native and in acquired immune response, play a major role in controlling synovium inflammation.

In line with the results of study of Sattar et al, in our study statins decreased articular tenderness, which these effects may be due to decrease of synovial T cells, antigen express and fibroblast-like synoviocyte release (36). Other hypothesis is the anti-inflammatory effect of statins that is due to decrease in the level of serum cholesterol. Several studies evaluated effects of other lipid lowering agents including fibrates and ezetimibe on rheumatoid arthritis and concluded this drug can decrease inflammation in rheumatoid arthritis. In our study after omitting bias effect of lipids, those groups that treated with statins decreased disease activity. The results of our study showed statins decreased the level of LDL-C, that this effect can decrease atherogenesis and cerebrovascular accidents in these patients and may be due to decrease inflammatory pathway. On the other hand, Abhari and colleagues showed that atorvastatin did not decrease the clinical and inflammatory markers in rheumatoid arthritis (37). This contradictory finding may be due to use of one kind of statin (atorvastatin). They also had not applied DAS-28 for evaluating disease activity, while patients were not evaluated duration of 1 and 7 months of the study.

Conclusion

The statins can decrease inflammation in rheumatoid arthritis and can be used for additive treatment in these patients.

Study limitations

The limitations of this study were the possible bias effect or interaction of disease-modifying antirheumatic drugs because these agents also have anti-inflammatory effects and can decrease cerebrovascular accidents (38). Another limitation was small size of the study. We suggest larger studies on this aspect of diabetic patients.

Authors' contribution

MK contributed to data interpretation and writing the paper. MS conceived the study idea and designed the study. RG contributed to data collection and preparation of the manuscript and submitting the manuscript. MOZHK participated in the evaluation of lipid profile. ZF performed data analysis. MG contributed to English editing.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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